ACUTE EFFECT OF PASSIVE SMOKING ON LUNG FUNCTION AND AIRWAY RESPONSIVENESS IN ASTHMATIC CHILDREN [a]

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Running title: Passive smoking in childhood asthma

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SUMMARY

In 11 children with bronchial asthma (age range 8-13 yr, 10 boys, 1 girl) we studied the effect of an one hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham. Nine of the subjects were on regular therapy with ihhaled $ß_2$-agonists and DSCG. Both components were withheld at least six hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations which caused a 100% increase in SRaw, $PC_{100}SRaw$, and a 20% fall in FEV_1, $PC_{20}FEV_1$. Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) cmH_2O*s, mean FEV_1 (SD) was 1.97 (0.32) and 1.98 (0.40) l, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) cmH_2O*s, mean FEV_1 (SD) was 1.95 (0.37) and 1.94 (0.35) l, respectively. Geometric mean (SD) $PC_{100}SRaw$ and $PC_{20}FEV_1$ after Sham was 1.39 (3.0) and 0.70 (2.7) mg/ml, after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively. There was no statistical difference in lung function and PC-values between Sham and passive cigarette smoking. The main symptoms during passive smoking were eye and nasopharyngeal irritation.

Our observations suggest that in children with mild bronchial asthma one hour of passive cigarette smoking does not cause airway obstruction or changes in bronchial responsiveness.

KEY WORDS:

Passive Smoking, Lung Function, Bronchial Hyperresponsiveness, Childhood Asthma

INTRODUCTION

Subjects with bronchial asthma are characterized by airway hyper-responsiveness to a variety of stimuli. Cigarette smoke is considered to be a common stimulus which may affect subjects with asthma (1-3).

In children, the adverse effect of chronic passive smoking on respiratory symptoms has received increasing attention (4-7). In some of these investigations an association between parental smoking habits and acute lower respiratory illness (8-12), respiratory symptoms (13-16), prevalence and severity of asthma (13,17,18), impaired lung function and bronchial responsiveness (10,12,13,16,17,19-23) could be demonstrated.

In contrast to chronic exposure, little is known on the acute effect of passive smoking in children. We therefore studied symptoms, lung function and airway responsiveness of children with bronchial asthma before and after one hour exposure to cigarette smoke as compared to control conditions.

MATERIAL AND METHODS

Patients

We investigated 11 children with allergic bronchial asthma (10 boys, 1 girl) ranging in age from 8 to 13 years (mean (SD) 10.4 (1.4) yr). Individual patient characteristics are given in table 1.

In all children the diagnosis of bronchial asthma was made up within at least 1 year before entering the study and patients had been followed up for a longer period of time on an out-patient basis. The children were not selected on the basis of symptoms induced by cigarette smoke.

Diagnosis was based on typical symptoms, reversible airflow obstruction, bronchial hyperresponsiveness to histamine and a positive prick skin test to at least one common allergen (Allergopharma, Reinbek, FRG). Six out of 11 patients showed an increase in total IgE (>150 IE/ml), and 6 children an increase of eosinophils in peripheral blood (>300/mm^3).

In all subjects the severity of asthma required a long-term therapy, which had to be continued in 9 of 11 children during the study period. All children on therapy received disodium cromoglycate, two puffs two to four times per day. Each puff of disodium cromoglycate (1 mg) was combined with 0.05 mg fenoterol (Ditec^R) or 0.5 mg reproterol (Aarane^R) as a $ß_2$-agonist. One subject took two additional puffs of 200 µg beclomethasone dipropionate. In all children, this therapeutic regime was sufficient to control the disease and allow normal activities. This is also reflected by the magnitude of morning (before therapy, PEF_{min}) and maximum daytime peak flow values (PEF_{max}), which were measured regulary (table 1).

In the 9 asthmatic children receiving regular therapy, the activity of the disease allowed to discontinue inhalation therapy at least six hours prior to each study session without precipitating symptoms or deteriorating lung function (subject 6 continued beclomethasone inhalation during the study period).

Spirometry, measured at least six hours after inhaling a bronchodilator was within normal limits. In all children the provocative concentration of inhaled histamine necessary to decrease FEV_1 by 20% as compared to baseline was less than 8 mg/ml (table 1), thus demonstrating airway hyperresponsiveness (see Histamine inhalation challenge).

During the study period and within the two weeks preceeding the study no child suffered from an upper respiratory tract infection, experienced an uncommon burden of allergen or reported on any other trigger which may worsen asthma; therefore all included children were considered to be currently clincally stable.

None of the children had ever actively smoked cigarettes, six of them were exposed to cigarette smoke at home (table 2).

Children and parents were informed about the aim of the study and gave their consent.

Cigarette smoke exposure

Exposure chamber

The study was performed in a 24 m^3 exposure chamber. To ensure homogenous concentration of cigarette smoke the air was moved by fans in

a spiral form. Sampling ports were distributed within the chamber to check for gradients of gas concentrations and particle density. Cigarette smoke was generated by a smoking machine designed in our laboratory which took 1 puff per cigarette per minute (according to DIN 10240). To achieve the target concentration of about 20 ppm CO, on average 2 cigarettes were smoked simultaneously. We used filter cigarettes of a leading brand with a nicotine content of 0.9 mg and tar content of 13 mg per cigarette.

Measurement of exposure conditions

The level of cigarette smoke exposure was determined by measuring CO, NO_x, particle density, nicotine, acetaldehyde, formaldehyde, acrolein and ammonia. Concentration of CO was measured continuously by an infrared gas analyzer (Unor 6N, Maihak AG, Hamburg, FRG) whose calibration was checked daily by a certified span gas (Linde AG, Unterschleißheim, FRG). Concentration of NO_x was measured by a chemiluminescence nitrogen oxides analyzer (8840, Monitor Labs Inc., San Diego, CA, USA) which was calibrated regularly by a permeation tube calibrator (Model 8550, Monitor Labs Inc., San Diego, CA). Particle density was monitored continuously by measuring optical particle density (RAM-1, GCA/Environmental Instruments, Bedford, Mass., USA) using a 4 µm precollector. Calibration of optical particle density was done in regular intervals gravimetrically by taking filter probes (Millipore, FALP 03700, Typ FA) from total sampling volumes of 17-73 litres of air. Nicotine, acetaldehyde, formaldehyde, acrolein and ammonia were determined using commercially available sample tubes and filters at sampling volumes ranging between 3 and 100 litres of air. Analysis was done by gas chromatography (nicotine), by high performance

liquid chromatography (acetaldehyde, formaldehyde, acrolein) and by the indophenol method VDI 2461 (ammonia). Temperature and relative humidity were measured at the beginning and at the end of each exposure.

Estimation of chronic smoke exposure

To estimate chronic passive smoke exposure at home, urinary cotinine concentrations were determined in triplicate from morning urine specimens collected at the second study day. Determination was made in an environment free of smoking. Urine was stored at -20 °C until assayed. Cotinine was measured by a radioimmunoassay procedure (24).

Assessment of symptoms

Before and immediately after exposure the chest of each subject was auscultated by one of us (M.O.). To estimate severity of symptoms induced by exposure, the children and their parents were instructed to check an ordinal scale ranging from 0 to 10 in order to determine severity of eye, nose irritation, throat irritation, cough, chest tightness and headache. Zero indicated no perceptible symptom, 10 almost intolerable severity of the respective symptom.

Lung Function Measurement

Airway resistance (Raw) during breathing at 1 Hz and thoracic gas volume (TGV) were measured by a volume-constant body plethysmograph (Bodytest, E. Jaeger, Würzburg, FRG) connected to a Computer (PDP 11/04, Digital Equipment Corp., Maynard, MA, USA). Airway resistance was multiplied by the corresponding thoracic gas volume to obtain specific airway resistance (SRaw). Airway resistance was measured during up to 4 breathing cycles. FEV_1 was assessed by a pneumotachygraph immediately after body plethysmography. Measurements were repeated 4 times. For analysis, the average of 4 values of SRaw and the average of the two maximum values of FEV_1 was taken.

Histamine Inhalation Challenge

Bronchial challenge with histamine was done according to the guidelines of Chai et al. (25) using a breath-synchronized pressure valve. The aerosols were generated during 0.6 sec. at the beginning of 5 slow inspirations from FRC to TLC, the nebulizer output being 80 µl of solution per 5 nebulizations. Saline solutions of histamine diphosphate (Sigma Chemie, Deisenhofen, FRG) were prepared daily. After inhaling buffer solution, the subjects inhaled doubling concentrations of histamine, starting with 0.05 mg/ml histamine. Lung function was measured 1 and 3 min after inhalation. The inhalation was stopped after at least a 100 % increase of SRaw and a 20 % fall in FEV_1. Dose-response curves were constructed by plotting SRaw and FEV_1 against log histamine concentration. By linear interpolation, the provocative

concentrations of histamine (in mg/ml) were computed necessary to increase SRaw by 100 % (PC_{100}SRaw) and to decrease FEV_1 by 20 % ($PC_{20}FEV_1$) as compared to baseline. With this method, hyperresponsiveness was assumed if PC-values were below 8 mg/ml (26).

Experimental Protocol

Each subject was studied at three days within a two week period. All investigations were performed at least six hours after the last application of therapy.

On the first day recent history was taken and a physical investigation performed. Lung function and airway responsiveness to inhaled histamine were measured. In case of stable clinical conditions, normal lung function and airway hyperresponsiveness, the children and their parents were instructed in the experimental procedure. They were provided with sampling probes for collecting morning urinary specimens.

On the second study day, exposure to ambient air (Sham) and at the third study day exposure to cigarette smoke was performed.

On exposure days, subjects rested for 10 minutes after entering the laboratory. After auscultation of the chest, assessment of symptoms and measurement of baseline lung function, the children entered the exposure chamber. They were always seated at the same place inside the chamber. Five minutes before the end of exposure, symptoms were assessed again. Immediately after exposure, auscultation of the chest and lung function measurement were performed. Histamine inhalation challenge was started 15 minutes after the end of exposure.

Statistical Analysis

Lung function parameters before and after both exposures and control values were compared to each other by the paired t-test after appropriate Bonferroni correction for multiplicity of tests (27). Log PC-values after both exposures and control values were also compared by the paired t-test. The assumption of normal distribution of data was checked by normal probability plots and tests. Statistical significance was assumed for $p<0.05$.

RESULTS

Exposure conditions

During Sham and cigarette smoke exposure, mean (SD) temperature was 24.1 (1.6) °C and mean relative humidity was 51 (3) %, with no difference between the study days. During passive smoke exposure, mean (SD) total particle density was 2743 (348) $\mu g/m^3$ and nicotine content was 397 (78) $\mu g/m^3$. Mean (SD) concentrations of CO were 20.5 (0.5) ppm, NO_x 0.90 (0.09) ppm, formaldehyde 0.13 (0.01) ppm, acetaldehyde 0.50 (0.05) ppm, acrolein 0.081 (0.017) ppm and ammonia 5.69 (3.35) ppm. During exposure with ambient air, mean (SD) CO was 0.1 (0.3) ppm, and mean (SD) total particle density was 17 (57) $\mu g/m^3$.

Symptoms during exposure

In all of our children, auscultation of the chest was normal before and after exposure to Sham and cigarette smoke, respectively. Eye irritation was experienced by all subjects during smoke exposure (Fig. 1). Nasal congestion was reported by 9/11 children after cigarette exposure and 5/11 after Sham. After smoke exposure, throat irritation occured in 3/11, cough in 0/11, chest tightness in 3/11, and headache in 3/11 children. Except for eye irritation, the frequency and intensity of the symptoms did not differ between cigarette smoke and Sham exposure (Fig. 1).

Variability of baseline lung function

Mean (SD) SRaw before Sham and smoke exposure was 8.7 (3.6) and 10.4 (5.3) $cmH_2O \cdot s$, respectively. These values were not significantly different from each other nor from the mean (SD) SRaw value of 8.5 (2.8) $cmH_2O \cdot s$ measured on study entry (control, table 3).

Mean (SD) FEV_1 before Sham and cigarette smoke was 1.97 (0.32) and 1.95 (0.39) l, respectively. These values were not significantly different from each other nor from the mean (SD) FEV_1 value of 1.95 (0.39) l when entering the study (control, table 3).

Mean (SD) values of individual variation coefficients of the three repeated determinations of SRaw and FEV_1 were 21 (11) and 6 (4) %, respectively.

Lung function changes during exposure

Mean (SD) SRaw before and after one hour exposure to ambient air (Sham) was 8.7 (3.6) and 9.0 (3.2) $cmH_2O \cdot s$, respectively, with no statistically significant difference (table 3). Mean (SD) FEV_1 before and after Sham was 1.97 (0.32) and 1.98 (0.40) l, respectively, with no significant difference. Percentage changes of SRaw and FEV_1 during Sham ranged from -28 to +59% and from -10 to +9%, respectively.

Mean (SD) SRaw before and after one hour exposure to cigarette smoke was 10.4 (5.3) and 9.4 (3.3) $cmH_2O \cdot s$, respectively. Mean (SD) FEV_1 before and after smoke exposure was 1.95 (0.39) and 1.94 (0.35) l, respectively (table 3, Fig. 2). Values before and after exposure were not significantly different from each other. Percentage changes of SRaw and FEV_1 during passive smoking ranged from -37 to +12% and from -25 to +13%, respectively.

Airway responsiveness during exposure

Geometric mean (SD) PC_{100}SRaw and $PC_{20}FEV_1$ at control were 0.85 (2.4) and 0.54 (2.7) mg/ml, respectively (table 4, Fig. 3).

Geometric mean (SD) PC_{100}SRaw and $PC_{20}FEV_1$ measured after Sham were 1.39 (3.0) and 0.70 (2.7) mg/ml, respectively. Geometric mean (SD) PC_{100}SRaw and $PC_{20}FEV_1$ after exposure to cigarette smoke were 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively (table 4, Fig. 3).

PC_{100}SRaw and $PC_{20}FEV_1$ were not significantly different between Sham, cigarette smoke exposure or control.

As determined from Sham and control, the mean (SD) value of individual variability of $PC_{100}SRaw$ and $PC_{20}FEV_1$ was 1.0 (0.5) and 0.9 (0.6) doubling concentrations of histamine, respectively.

DISCUSSION

Our observations demonstrate that in children with mild bronchial asthma one hour passive smoking produced mainly eye irritation but no airway obstruction and no significant changes in bronchial responsiveness to inhaled histamine.

To the best of our knowledge, acute pulmonary response to passive smoke exposure has not been studied in asthmatic children. Previous studies on the acute effect of passive smoking were performed in adult asthmatics. These studies showed conflicting results.

Shephard and coworkers (28) investigated 14 asthmatic subjects during a 2-h cigarette smoke exposure (24 ppm CO) and observed no significant changes in pulmonary function. Dahms et al. (29) reported on 10 asthmatics passively exposed to cigarette smoke (15 - 20 ppm CO) for one hour. These authors found a 21.4% decrease in FEV_1 following smoke exposure in asthmatics compared to normal controls. Knight and Breslin (30) studied 6 patients with asthma who developed a 11% decline in FEV_1 and an increase in bronchial reactivity to inhaled histamine 4 hours after a 1-h smoke exposure (15 - 25 ppm CO). Wiedemann and coworkers (31) examined the acute effect of a 1-h chamber exposure to cigarette smoke (40 - 50 ppm CO) on lung function and airway responsiveness in 9 adult asthmatics. In these subjects no change in lung function was observed, but a small decrease in nonspecific airway

reactivity. Recently, Stankus et al. (32) investigated the effect of an 2 hour exposure to tobacco smoke (8.7 - 14.1 ppm CO) in 21 subjects with asthma who claimed on respiratory symptoms on previous exposure to cigarette smoke. In 7 of these 21 subjects suspected as smoke sensitive asthmatics, they found a significant (> 20%) fall in FEV_1. These findings in adult asthmatics demonstrate that there might be a subgroup of smoke sensitive asthmatics who develop acute airway obstruction without consistent changes in airway responsiveness following passive smoke exposure.

In our group of asthmatic children, after exposure to Sham changes of FEV_1 between -10 and +9% were observed as compared to pre-exposure values. After exposure to passive cigarette smoke, in 9 subjects changes of FEV_1 were within this range. Subject #3 showed an increase in FEV_1 by 13% after smoke exposure in contrast to an decrease of 10% after Sham. Subject #7 showed a decrease in FEV_1 by 25% after smoke exposure as compared to an increase of 5% after Sham. In both subjects, changes in FEV_1 were larger than corresponding changes in SRaw. Analysis of the spirometric curves, however, did not reveal any sign of deficient cooperation in both subjects. According to our study protocol, baseline lung function measurement was performed three times on three different study days. Mean coefficients of variation were 6% for FEV_1 and 21% for SRaw which is well within the reproducibility reported in adult subjects (33). Therefore, we do not believe that our inability to demonstrate an adverse acute effect of passive cigarette smoking on lung function was due to an insufficient reproducibility of lung function data.

Airway hyperresponsiveness to inhaled histamine in terms of $PC_{20}FEV_1$ and $PC_{100}SRaw$ was assessed three times on three different study days. The two challenges without previous smoke exposure (control, Sham) showed a variability of plus minus one doubling concentration of histamine, which is

within accepted limits (33,34). Therefore, it is unlikely that our findings were due to a weak reproducibility of bronchial responsiveness measurement. However, it seems to us that in children further investigations on the possible interaction between DSCG and passive smoking should be done.

Nine out of 11 asthmatic children were under regular therapy consisting of inhaled β_2-agonists and disodium cromoglycate (and in subject #6 of additive 400 µg beclomethasone diproprionate). The duration of the effect of inhaled β_2-agonists on airway tone and bronchial responsiveness is within 3 - 5 hours (35). Therefore, as we started exposure at least 6 hours after the last inhalation therapy, an influence of β_2-agonists on our data seems to be unlikely.

This may however not be true for disodium cromoglycate (DSCG). There are conflicting data on the protective effect of DSCG on airway responsiveness. Most authors agree that a significant protection against airway obstruction induced by histamine or methacholine could not be substantiated (36). Recently it has been shown that long term treatment with DSCG may modify the level of bronchial hyperresponsiveness (37).

In our study all children showed bronchial hyperresponsiveness to inhaled histamine, irrespective of the foregoing therapy with DSCG. Three of the 9 children with DSCG showed an increase in airway responsiveness after passive cigarette smoking, the remaining children an decrease in airway responsiveness. In comparison, one child without therapy showed an increase and the other one without therapy showed a decrease in hyperresponsiveness after smoke exposure. Our inability to demonstrate an effect of passive smoke exposure on airway responsiveness in the presence of hyperresponsiveness to inhaled histamine is unlikely to be explained by the pharmacologic profile of DSCG.

In the present study the level of cigarette smoke exposure was characterized by several components which may be potential irritants per se. It has been suggested that substances like CO (38), NO_2 (39), formaldehyde (40) and aerosolized nicotine (41) may produce upper respiratory symptoms. The threshold concentration of NO_2 which causes an increase in hyper-responsiveness during resting ventilation is about 0.25 ppm (39). In our experiments, total NO_x concentration was about 1 ppm, however, the reactive component NO_2 was measured to be less than 3% of the total concentration of NO_x. Acrolein (an unsaturated aldehyde) has been demonstrated to decrease pulmonary function in guinea pigs at concentrations of at least 0.31 ppm and to produce transient bronchial hyperresponsiveness (42,43). In our study the concentration of acrolein was in the range of 0.1 ppm. For saturated aldehydes like formaldehyde it has been reported that in asthmatics exposure to concentrations up to 3 ppm for 1 - 1.5 hour did not cause statistically significant decrements in pulmonary function (40,44). Under our exposure conditions, formaldehyde concentration was about 0.13 ppm. Therefore, our concentrations of the cigarette smoke components were always lower than those effective in the single component exposure studies. Because we did not see an effect of passive smoking on lung function or airway responsiveness, synergistic effects between the constituents of cigarette smoke seems to be unlikely.

By measuring urinary cotinine concentration which is an accepted biological marker of chronic exposure to passive smoke (45-48), we were able to identify 6 out of 11 asthmatic children with reported passive smoke exposure at home (table 2). This observation confirms that many children are exposed by the smoking habits of their parents. Since the purpose of our study was to investigate the acute effects of passive smoking and since we did not find an

effect and could not identify an active component of cigarette smoke in our experiments, it is difficult to compare our data with those of chronic exposure studies. Chronic exposure has been demonstrated to increase bronchial responsiveness and to impair lung function (10,12,13,16,17,19-23). Our data regarding short-term exposure are by no means contradictory to these observations. In addition, chronic passive smoke exposure may induce changes in the airways which mask airway response to acute exposure. From our data this hypothesis can not be proved, however, it would be of interest to study the acute airway response of asthmatic children with and without chronic smoke exposure.

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LEGENDS TO FIGURES

Figure 1 Median and 90%-percentil of symptom score after Sham and passive smoke exposure.

Figure 2 FEV_1 (l) and SRaw ($cmH_2O \cdot s$) before and after exposure (Sham, Passive Smoking) and at the control day.

Figure 3 Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

Legend to Table 1:

[a]VC: inspired vital capacity.

[b]Geometric mean values and geometric standard deviations of mean.

[c]Therapy: B = inhaled beta-2-agonists, D = disodium cromoglycate, Ci = inhaled corticosteroids.

For definitions see text.

Legend to Table 4:

[a]Geometric mean values and geometric standard deviations of mean.

TABLE 1 - Individual data of patients

Patient No.	Sex	Age yr	Weight kg	Height cm	Atopy	IgE IE/ml	Eosinophils counts/mm^3	PEF_{min} l/min	PEF_{max} l/min	VC[a] l_{BTPS}	FEV_1 %pred	$PC_{20}FEV_1$[b] mg/ml	Therapy[c]
1	m	12	50	165	+	92	563	400	480	3.68	97	0.09	B,D
2	m	13	42	154	+	114	350	280	330	2.18	76	0.34	B,D
3	m	11	35	142	+	524	422	320	440	2.35	97	0.73	B,D
4	m	9	38	140	+	219	100	300	380	2.46	110	1.25	B,D
5	m	10	35	150	+	518	441	280	340	2.48	88	1.72	B,D
6	m	11	40	149	+	146	319	300	380	2.60	111	1.02	B,D,iC
7	m	11	41	151	+	101	181	330	400	2.60	107	1.13	B,D
8	m	9	40	141	+	269	143	240	270	1.90	85	0.12	B,D
9	m	8	26	137	+	137	147	210	330	1.82	90	1.28	-
10	m	10	36	142	+	361	422	280	350	3.00	130	0.46	B,D
11	w	10	35	143	+	185	293	150	220	2.20	98	0.30	-
Mean		10.4	38	147		242	307	281	356	2.48	99	0.77	
SD		1.4	6	8		159	149	65	73	0.52	15	0.55	

TABLE 2 - Urinary cotinine concentration and reported parental smoking habits

Patient No.	cotinine (ng/ml)	paternal smoking	maternal smoking
1	11	+	-
2	8	+	-
3	34	-	-
4	4	+	-
5	2	-	-
6	1	-	+
7	3	-	+
8	0	-	-
9	11	+	-
10	0	-	-
11	0	-	-

TABLE 3 - SRaw (in $cmH_2O \cdot s$) and FEV_1 (in l) before (pre) and after (post) exposure to ambient air (Sham) or passive smoke and at the control day

	CONTROL		SHAM				PASSIVE SMOKE			
Patient No.	SRaw	FEV_1	SRaw		FEV_1		SRaw		FEV_1	
			pre	post	pre	post	pre	post	pre	post
1	13.2	2.68	12.5	10.6	2.60	2.84	9.9	11.1	2.76	2.81
2	8.1	1.74	5.9	7.9	1.93	1.86	8.6	9.4	1.84	1.82
3	10.7	1.75	12.6	12.8	1.75	1.57	9.6	8.8	1.74	1.97
4	10.1	1.90	4.6	7.3	2.13	2.11	11.1	9.3	1.83	1.84
5	10.5	1.86	11.9	12.7	1.71	1.75	14.3	14.0	1.47	1.55
6	8.1	2.30	9.0	7.8	2.27	2.32	10.5	8.8	2.23	2.26
7	5.2	2.28	5.8	4.2	2.21	2.33	4.6	4.4	2.33	1.74
8	4.0	1.52	6.6	7.2	1.76	1.75	6.4	6.2	1.79	1.78
9	5.4	1.47	3.5	4.4	1.82	1.69	5.5	5.4	1.59	1.72
10	10.8	2.33	13.9	13.0	2.07	2.10	23.9	15.0	2.21	2.13
11	7.8	1.64	9.7	10.6	1.47	1.50	9.7	10.6	1.63	1.71
Mean	8.5	1.95	8.7	9.0	1.97	1.98	10.4	9.4	1.95	1.94
SD	2.8	0.39	3.6	3.2	0.32	0.40	5.3	3.3	0.39	0.35

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TABLE 4 - Histamine concentration (mg/ml) necessary to increase SRaw by 100% ($PC_{100}SRaw$) or to decrease FEV_1 by 20% ($PC_{20}FEV_1$) after 1 hour exposure to ambient air (Sham) or to passive smoke and at the control day

	CONTROL		SHAM		PASSIVE SMOKE	
Patient No.	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$	$PC_{100}SRaw$	$PC_{20}FEV_1$
1	0.25	0.09	0.51	0.27	0.30	0.21
2	0.92	0.34	5.81	0.78	6.40	1.10
3	1.60	0.73	0.38	0.11	1.24	1.05
4	1.12	1.25	2.38	0.79	1.17	0.87
5	1.45	1.72	4.59	1.68	3.16	2.64
6	2.12	1.02	3.83	1.71	6.90	3.03
7	1.07	1.13	0.59	0.60	1.45	1.57
8	0.12	0.12	0.62	0.67	1.01	1.14
9	1.85	1.28	4.80	4.22	1.40	0.75
10	0.81	0.46	0.37	0.33	0.70	0.27
11	0.66	0.30	1.24	0.68	2.79	1.00
Mean[a]	0.85	0.54	1.39	0.70	1.65	0.96
SD	2.40	2.70	3.00	2.70	2.50	2.30

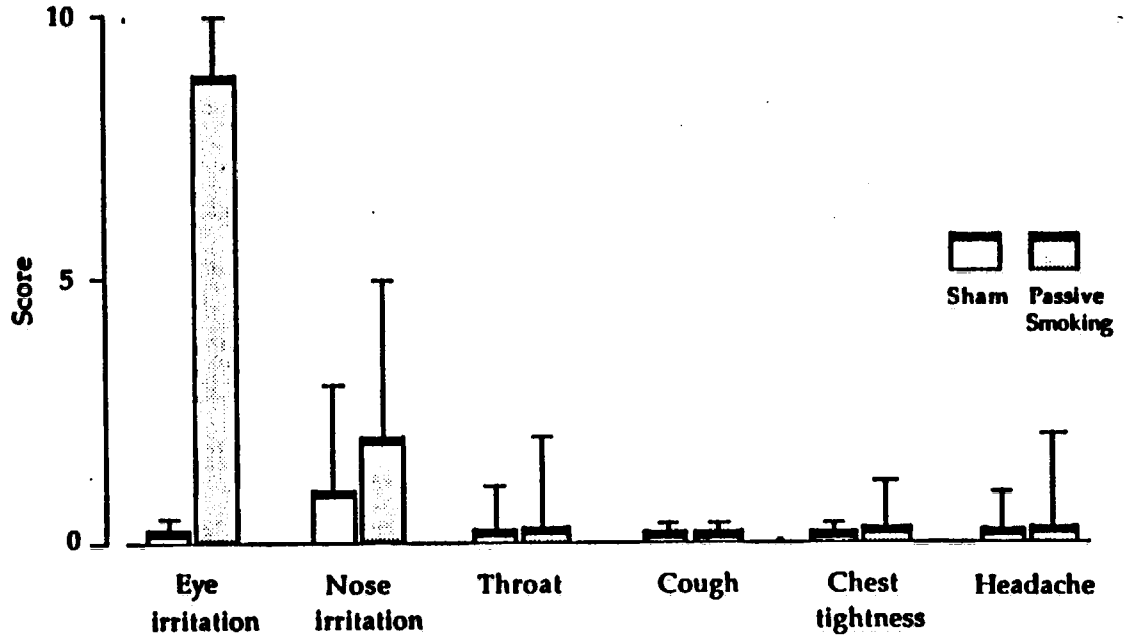

Fig. 1. Median and 90%-percentil of symptom score after Sham and passive smoke exposure.

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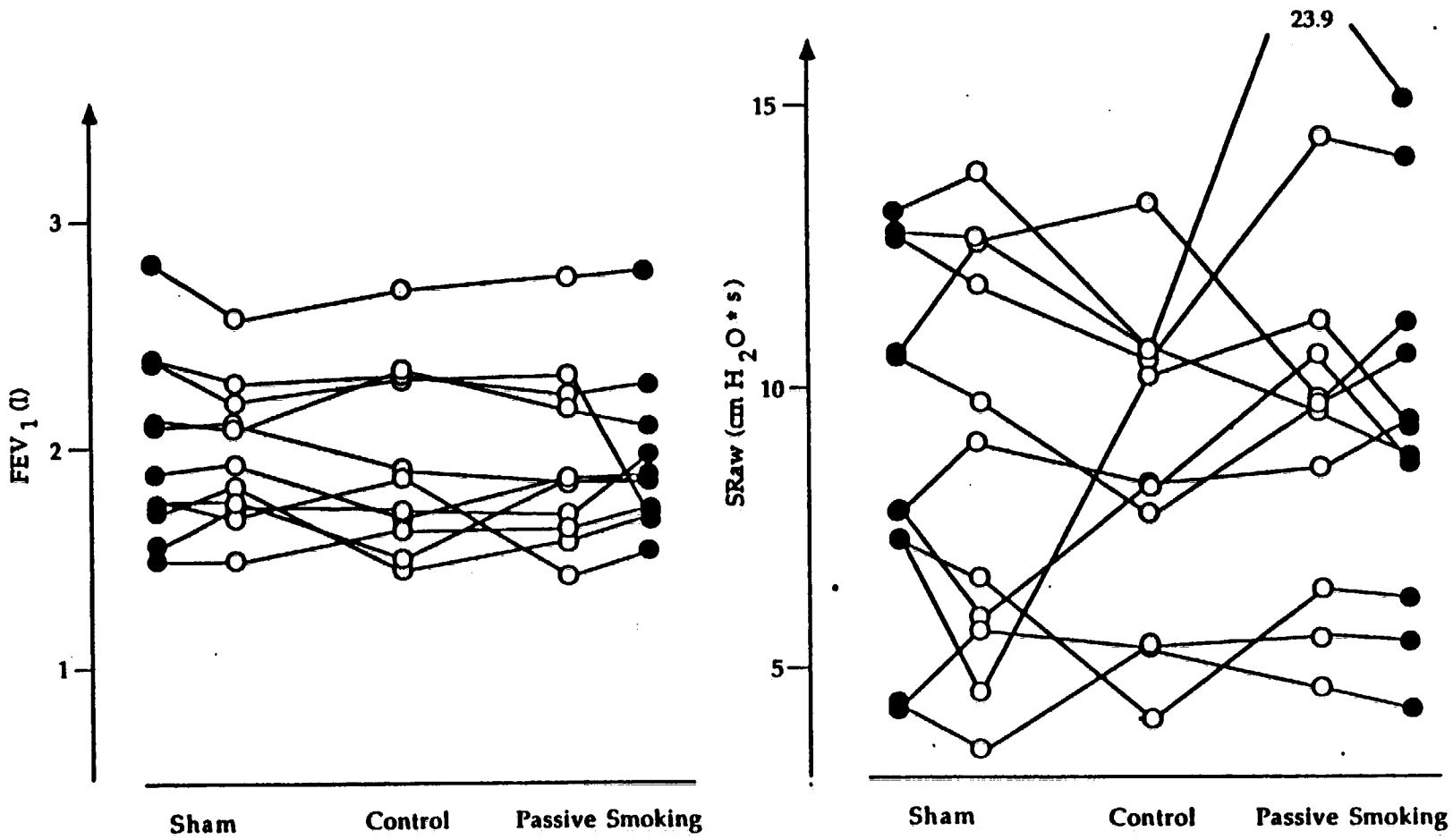

Fig. 2. FEV_1 (l) and SRaw (cmH_2O*s) before (○) and after (●) exposure (Sham, Passive Smoking) and at the control day (○).

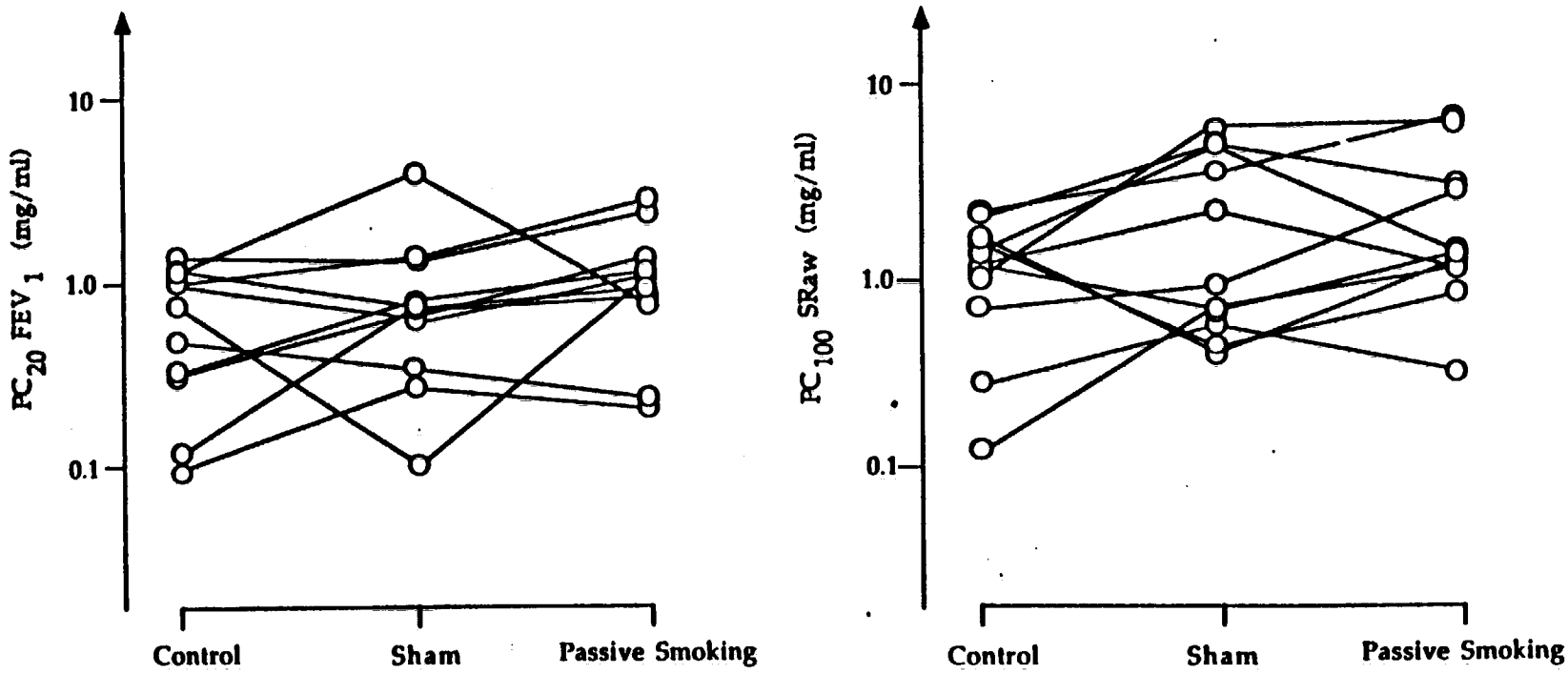

Fig. 3. Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

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